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Visible Light-Driven Strain-Increase Ring Contraction Allows the Synthesis of Cyclobutyl Boronic Esters

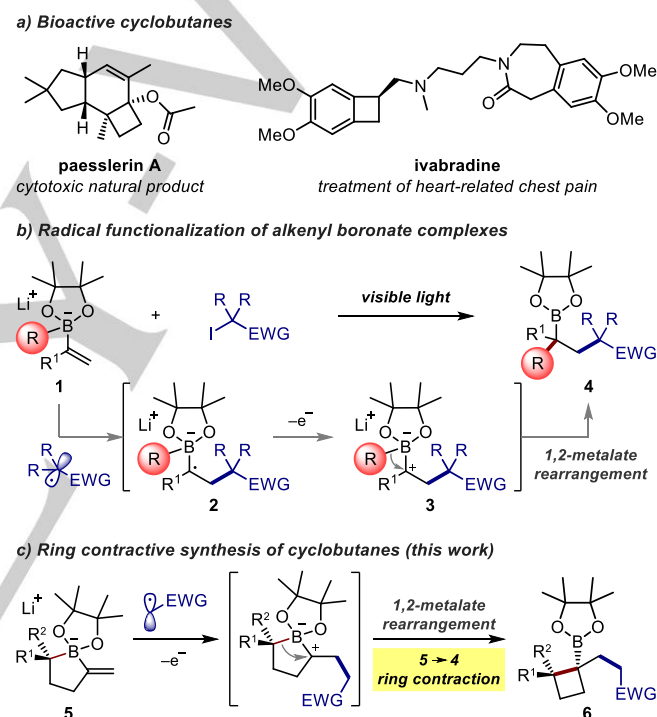
Raffael Davenport, Mattia Silvi, Adam Noble, Zied Hosni, Natalie Fey and Varinder K. Aggarwal*

Abstract: There are a limited number of ring contraction methodologies which convert readily available 5-membered rings into strained 4-membered rings. Here we report a photo-induced radical-mediated ring contraction of 5-membered ring alkenyl boronate complexes into cyclobutanes. The process involves addition of an electrophilic radical to the electron-rich alkenyl boronate complex, leading to an α -boryl radical. Upon one-electron oxidation, ring-contractive 1,2-metalate rearrangement occurs to give a cyclobutyl boronic ester. A range of radical precursors and vinyl boronates can be employed, and chiral cyclobutanes can be accessed with high levels of stereocontrol. The process was extended to the preparation of benzo-fused cyclobutenes and the versatility of the boronic ester was demonstrated by conversion to other functional groups.

Cyclobutanes are commonly occurring structural motifs, which are finding increasing applications in medicinal chemistry owing to their diverse bioactivities (Scheme 1a).^[1,2] This is attributed to their structural rigidity, which provides a well-defined spatial arrangement of their substituents.^[3] Whilst a number of methods for the synthesis of cyclobutanes have been reported, only a few different strategies have been described, such as [2+2] cycloadditions, 1,4-cyclization reactions, or ring expansion of cyclopropanes.^[4] A much less explored strategy is ring contraction from a 5- to 4-membered ring, which is particularly attractive because it converts one of the easiest to make ring sizes into one of the most difficult.^[4a,5] However, this approach is challenging due to the increase in strain energy between the substrate and the product, which has limited the scope of methodologies that can be applied, as they generally rely on the release of high energy by-products, such as in the photochemical Wolff rearrangement.^[6]

We, and others, recently reported that alkenyl boronates **1** readily react with electrophilic radicals to give highly functionalized boronic ester products **4** (Scheme 1b).^[7,8] The reaction proceeds via radical anion intermediates **2**, which undergo single-electron oxidation to zwitterionic species **3**, triggering a 1,2-metalate rearrangement. We reasoned that if cyclic 5-membered ring alkenyl boronates **5** were used, application of a similar strategy should lead to cyclobutanes **6** via ring contraction, providing there was sufficient driving force in the 1,2-metalate rearrangement to overcome the increase in strain

energy (Scheme 1c).^[9] Herein, we report the development of a novel visible light-induced strain-increasing 5 \rightarrow 4 ring contraction. Furthermore, a variety of cyclobutyl boronic esters can be accessed in high yields and with excellent stereocontrol, including those with contiguous quaternary stereocenters and substantially more strained benzo-fused cyclobutenes.^[10]



Scheme 1. a) Cyclobutenes in natural product and drugs. b) Radical reactivity of alkenyl boronate complexes. c) Proposed ring contractive synthesis of cyclobutyl boronic esters.

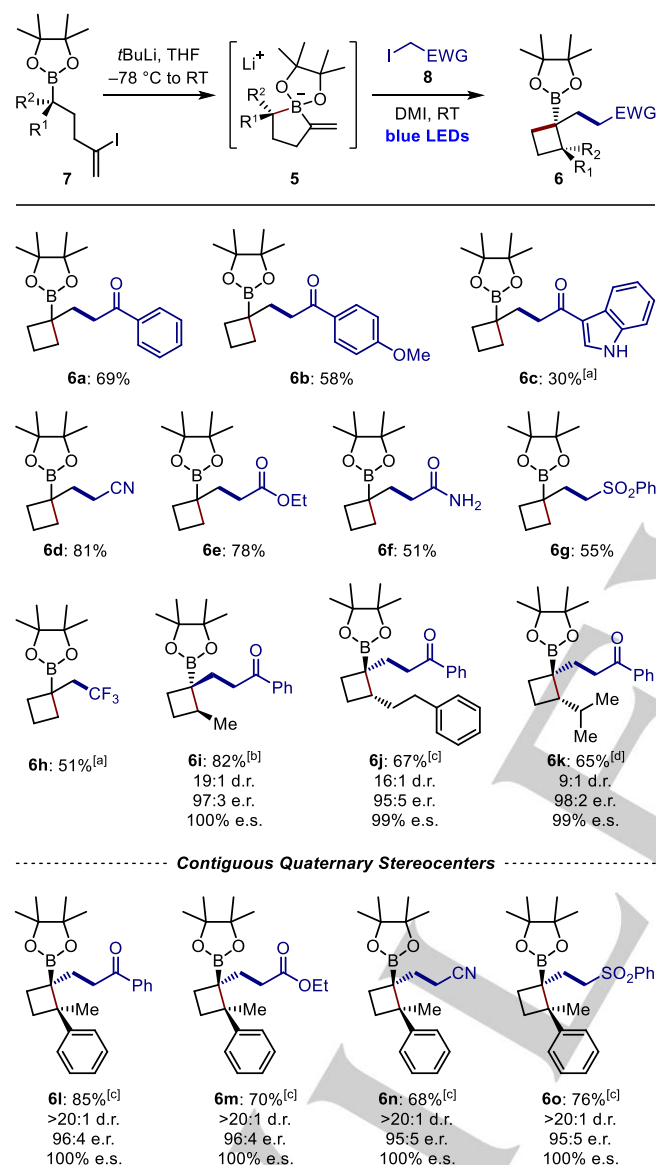
Our investigations initially focused on designing a reliable route to cyclic 5-membered ring alkenyl boronate complexes. We found that boronate complex **5** ($R^1 = R^2 = H$) could be formed quantitatively upon treatment of a THF solution of the bench-stable and easily accessible alkenyl iodide **7** with $t\text{BuLi}$ at -78°C (Scheme 2, see SI for further details). Subsequent addition of a solution of iodoacetophenone in 1,3-dimethyl-2-imidazolidinone (DMI) at RT and irradiation using blue LEDs^[7b] led to the formation of the desired geminal-disubstituted cyclobutane product **6a** in good yield. Having identified suitable conditions, we investigated the generality of the reaction by testing different alkyl iodide radical precursors **8**. A variety of α -iodoketones could be employed to provide **6a-c** in moderate to good yields. Cyclobutyl boronic esters substituted with synthetically versatile nitrile, ester

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and amide moieties (**6d-f**) were prepared in good yields from the corresponding alkyl iodides. Sulfone **6g** could also be efficiently synthesized, providing additional opportunities for product manipulation.^[11] Finally, cyclobutane **6h** bearing a trifluoromethyl group, a privileged motif in medicinal chemistry,^[12] could be synthesized in synthetically useful yield from commercially available CF_3I -2DMSO complex.^[13]



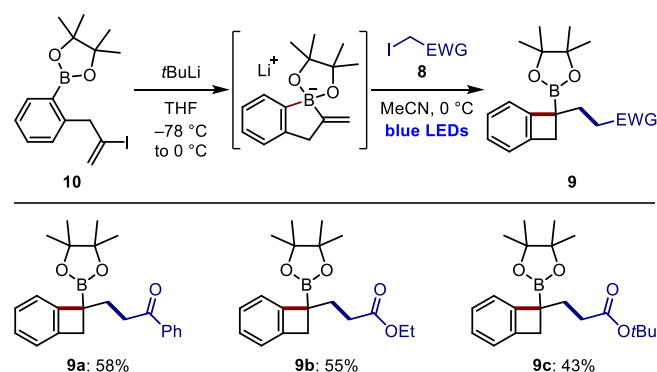
Scheme 2. Investigation of the reaction scope. All values refer to isolated yields from reactions performed on a 0.3 or 0.2 mmol scale, using 1 equiv of boronic ester, 2.1 equiv of $t\text{BuLi}$, and 1.5 equiv of alkyl iodide under Schlenk techniques. See SI for full experimental details. [a] $\text{Ru}(\text{bpy})_3\text{Cl}_2$ (1 mol%) was used. [b] Photochemical step carried out in EtCN at -60°C . [c] Photochemical step carried out in EtCN at -60°C and solvent exchange from THF to EtCN performed at -40°C . [d] Photochemical step carried out in THF at -78°C .

Encouraged by the broad scope of radical precursors that could be used, we sought to extend our methodology to the

stereocontrolled synthesis of chiral polysubstituted cyclobutyl boronic esters. Under slightly modified reaction conditions,^[14] we found that enantioenriched secondary boronic esters (readily prepared through lithiation–borylation methodology)^[15] bearing substituents of varying steric demand at the α -position afforded 1,1,2-trisubstituted cyclobutyl boronic esters **6i-k** in good to excellent yield (Scheme 2). Pleasingly, in addition to the 1,2-migration occurring with complete stereospecificity with respect to the migrating carbon, the newly generated quaternary stereocenters were formed with high levels of diastereoselectivity, thus providing **6i-k** with excellent enantio- and diastereocontrol.

We also explored the potential of this methodology for the asymmetric construction of *contiguous* quaternary stereocenters, which presents a considerable synthetic challenge.^[16] In the context of cyclobutane synthesis, there is additional strain imparted by creating adjacent quaternary centers, which must be compensated for in the 1,2-metalate rearrangement. Using readily available enantioenriched tertiary boronic esters, we found that our methodology enabled efficient access to cyclobutane **6l**, featuring two contiguous quaternary stereocenters, in high yield and with *complete diastereo-* and *enantiocontrol* (Scheme 2). The process was successfully extended to other radical precursors bearing ester, nitrile and sulfone substituents, giving cyclobutanes **6m-o**, again with complete stereocontrol.

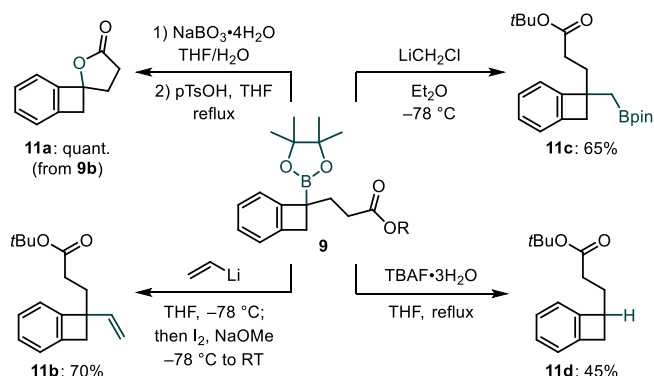
Having found that there was indeed sufficient driving force in the 1,2-metalate rearrangement to overcome the increase in strain energy going from a 5- to a 4-membered ring, including those bearing contiguous quaternary centers, we sought to test the limit of our methodology in the synthesis of benzo-fused cyclobutenes. These motifs are generally more difficult to access than saturated cyclobutenes due to their enhanced strain energy (6 kcal mol^{-1} higher).^[10,17] In practice, after a brief optimization of the reaction parameters in the photochemical step (MeCN, 0°C ; see SI for details), we found that benzo-fused cyclobutenes **9a-c**, decorated with a versatile boronic ester moiety and different functional groups, could be readily prepared in synthetically useful yields from aryl boronic ester **10** (Scheme 3).



Scheme 3. Synthesis of benzannulated cyclobutene boronic esters. All values refer to isolated yields from reactions performed on a 0.2 mmol scale, using 1 equiv of boronic ester, 2.1 equiv of $t\text{BuLi}$, and 1.5 equiv of alkyl iodide under Schlenk techniques. See SI for full experimental details.

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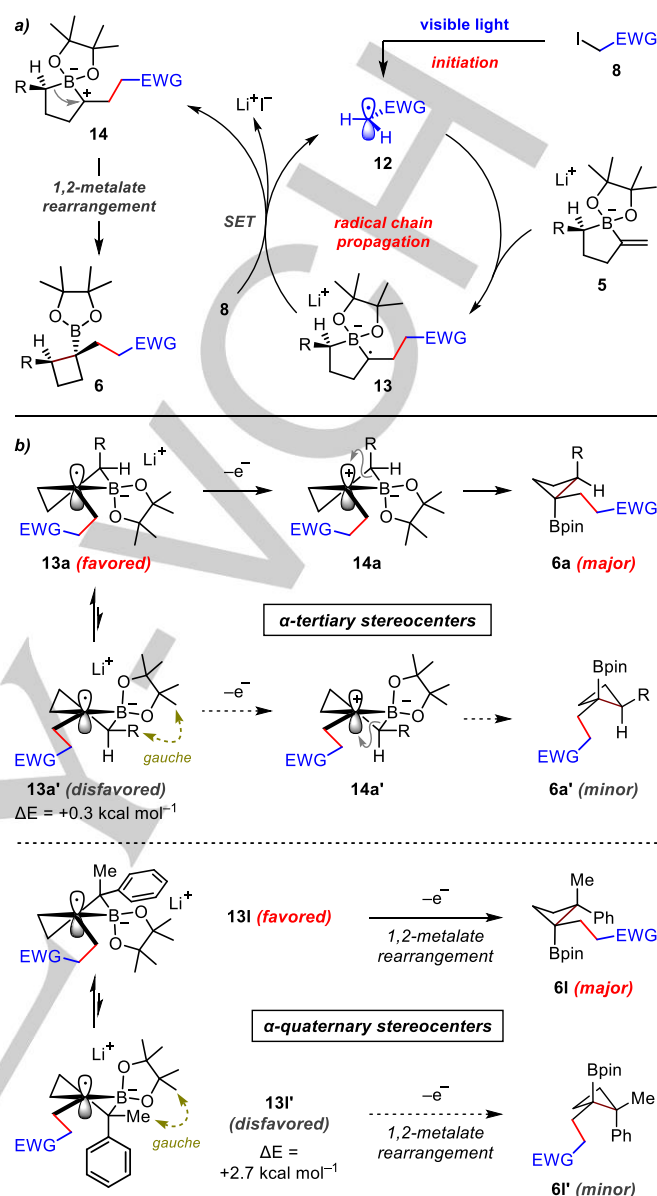
Finally, we explored the versatility of the boronic ester moiety in the benzo-fused cyclobutenes since functionalization of less strained cyclobutyl boronic esters has already been described.^[8,18] As depicted in Scheme 4, spiro-lactone **11a** could be quantitatively prepared by an oxidation/lactonization sequence.^[19] Zweifel olefination^[20] or Matteson homologation^[21] enabled the construction of new C–C bonds, leading to alkene **11b** and boronic ester **11c** in good yields, respectively. Finally, fluoride-induced protodeboronation gave benzo-fused cyclobutene **11d**.^[22]



Scheme 4: Product derivatization. See SI for full experimental details.

We propose that the mechanism of our cyclobutane synthesis resembles the radical reactivity of acyclic vinyl boronate complexes.^[7b] As depicted in Scheme 5a, visible light-induced homolytic cleavage of the carbon–iodine bond in alkyl iodide **8** leads to electrophilic radical **12**, which readily adds to the electron-rich double bond within boronate complex **5**, giving spirocyclic radical anion **13**. Single-electron transfer (SET) from this electron-rich species to the electron-deficient alkyl iodide **8** regenerates **12** to propagate the radical chain, and forms zwitterionic intermediate **14**, triggering a 1,2-metalate ring contraction to afford cyclobutane **6**.

In reactions of substrates with stereocenters α to the boronic ester, we believe that the stereoselectivity is dictated by the preferred conformation of the radical intermediates. Our preliminary computational studies (B3LYP/6-31G*, see SI for full computational details and discussion) suggest that the selectivity gets “locked in” between **13** and the 1,2-metalate rearrangement step, which is likely fast, as the product **6** is predicted to be thermodynamically very favourable. For both tertiary and quaternary stereocenters, a destabilizing gauche interaction between the pinacol moiety and the alkyl substituent occurs in the disfavoured conformers (**13a'** and **13l'** respectively). The energy difference between **13a** and **13a'** conformers is calculated to be very small, suggesting that other effects may play a role e.g. interactions between a lithium-solvent cluster and the EWG. Indeed, in strongly co-ordinating solvents (e.g. THF) the selectivity is considerably lower (2.4:1 vs >20:1 in EtCN; see SI for details). More detailed studies of the interactions with the lithium counterion will be needed to fully evaluate the balance of competing effects.



Scheme 5. Proposed reaction mechanism and stereochemical models. Calculated energy differences are potential energies (B3LYP/6-31G*, acetonitrile solvated) with R = Me for **13a/13a'** and using a methyl group in place of the (CH₂)₂EWG for **13l/13l'**. See SI for full computational details and discussion.

In conclusion, we have reported the synthesis of a variety of cyclobutyl boronic esters through a rare 5 → 4 ring contraction strategy triggered by a 1,2-metalate rearrangement. The process conveniently occurs under visible light irradiation and affords geminal and 1,2-substituted cyclobutyl boronic esters in high yield and excellent stereocontrol. Remarkably, this methodology enables the construction of contiguous quaternary stereocenters and benzannulated motifs, opening up new chemical space for drug design.

Acknowledgements

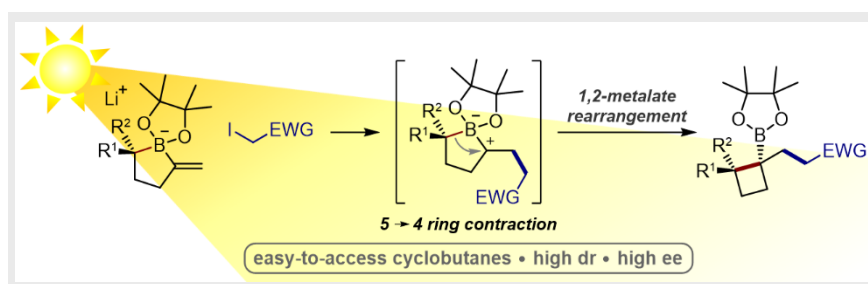
We thank the University of Bristol for financial support. R.D. thanks the Swiss National Science Foundation fellowship program (P2EZP2_175145). M.S. thanks the EU for H-2020 Marie Skłodowska-Curie Fellowship (grant no. 744242).

Keywords: Photoredox catalysis • Boron chemistry • Ring contraction • Metalate rearrangement • Cyclobutanes

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Easy to access cyclic vinyl boronate complexes undergo a strain-increase ring contraction through reaction with electrophilic radicals generated by visible light. A variety of cyclobutyl boronic esters can be obtained in high yields and excellent stereocontrol, including those containing contiguous quaternary stereocenters and also substantially more strained benzo-fused cyclobutenes.